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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/698,323	10/27/2000	Jeffrey M. Isner	47624-DIV (1417)	6299

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EXAMINER	
NGUYEN, QUANG	

ART UNIT	PAPER NUMBER
1633	

DATE MAILED: 08/09/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/698,323	ISNER ET AL.	
	Examiner	Art Unit	
	Quang Nguyen, Ph.D.	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 October 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *50,52,55-63,65-68,70,72-79 and 82-84* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *72-78* is/are allowed.

6)☒ Claim(s) *50, 52, 55-63, 65-68, 70, 79 and 82-84* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicant's amendment filed on 10/18/05 was entered.

Amended claims 50, 52, 55-63, 65-68, 70, 72-79 and 82-84 are pending in the present application, and they are examined on the merits herein.

Claim Objections

Claim 50 is objected to because of the term "fragement" which is misspelled. Appropriate correction is required.

Priority

The present application is a division of U.S. Serial No. 09/265,041, filed March 09, 1999, which claims benefit of the provisional application 60/077,262, filed March 09, 1998.

Upon review of the specifications of the U.S. Serial No. 09/265,041 and 60/077,262 applications and comparison with the specification of the present application, it is determined that pending claims with specific embodiments drawn to a method for inducing formation of new blood vessels in a mammal having chronic or acute ischemia, wherein the method comprises administering to the mammal an effective amount of a VEGF or a hematopoeitic factor other than GM-CSF sufficient to form the new blood vessels in the mammals, and increasing endothelial progenitor cell (EPC) frequency are only entitled to the priority benefit of the filing date of 03/09/1999. This is because the provisional application 60/077,262, filed on 3/9/1998, does not have

a written support for the use of VEGF or any hematopoietic factor other than GM-CSF to mobilize EPC or increasing endothelial progenitor cell frequency (see at least Summary of the Invention of pages 3-4; and the definitions of the terms "angiogenic protein" (on page 8, second paragraph) and "endothelial cell mitogen" (on page 11, fourth paragraph).

Furthermore, pending claims with specific embodiments directed to a hematopoietic factor which is angiopoietin-2, SCF or FLT-3 ligand, or an effective fragment thereof are only entitled to the priority benefit of the filing date of 03/09/1999. This is because nowhere in the provisional application, there is a disclosure for the use of angiopoietin-2, SCF and FLT-3 ligand or a fragment thereof in the methods as now claimed.

Accordingly, claims 50, 55-63, 65-68, 70, 79 and 82-84 are only entitled to the priority benefit of the filing date of 03/09/1999, whereas claims 52 and 72-78 are entitled to the priority benefit of the filing date of 03/09/1998.

Claim Rejections - 35 USC § 112

Claims 50, 55-56, 58-63, 65-68, 70 and 82-84 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for inducing formation of new blood vessels in a mammal having chronic or acute ischemia, wherein the method comprises administering to the mammal an effective amount of a vascular endothelial growth factor or a hematopoietic factor sufficient to form the new blood vessels in the mammal, and increasing endothelial progenitor cell frequency by at

least about 20% as determined by a standard EPC isolation assay, wherein the hematopoieitic factor is a GM-CSF, SCF, SDF-1, G-CSF, M-CSF, angiopoietin-1, or an effective fragment thereof;

does not reasonably provide enablement for a method for inducing formation of new blood vessels in a mammal having chronic or acute ischemia, wherein the method comprises administering to the mammal an effective amount of angiopoietin-2 or FLT-3 ligand or an effective fragment thereof. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims. ***This is a new ground of rejection.***

The factors to be considered in the determination of an enabling disclosure have been summarized as the quantity of experimentation necessary, the amount of direction or guidance presented, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art and the breadth of the claims. *Ex parte Forman*, (230 USPQ 546 (Bd Pat. Appl & Unt, 1986); *In re Wands*, 858 F.2d 731, 8 USPQ 2d 1400 (Fed. Cir. 1988)).

The instant disclosure is not enabled for the instant broadly claimed invention for the reasons discussed below.

1. The breadth of the claims

The instant claims encompass a method for inducing formation of new blood vessels in a mammal having chronic or acute ischemia, wherein the method comprises administering to the mammal an effective amount of a vascular endothelial growth factor

or a hematopoietic factor sufficient to form the new blood vessels in the mammal, and increasing endothelial progenitor cell frequency by at least about 20% as determined by a standard EPC isolation assay, wherein the hematopoietic factor is a GM-CSF, SCF, SDF-1, G-CSF, M-CSF, angiopoietin-1, angiopoeitin-2, FLT-3 ligand or an effective fragment thereof.

2. The state and unpredictability of the prior art

At about the effective filing date of the present application, virtually little was known on the use of angiopoietin-2 and/or FLT-3 ligand and/or their fragments thereof for the induction of new blood vessels and for increasing endothelial progenitor cell frequency by at least about 20% as determined by a standard EPC isolation assay in a mammal having chronic or acute ischemia as evidenced at least by the teachings of Hammond et al. (U.S. Patent 5,880,090; Cited previously), Isner et al. (U.S. Patent No. 5,980,887), Witzenbichler et al. (J. Biol. Chem. 273:18514-18521, 1998); Asahara et al. (EMBO J. 18 :3964-3972, 1999). On the contrary, Witzenbichler et al describes angiopoietin-2 is a putative natural antagonist of angiopoieitin-1, and that unlike angiopoietin-2 lacks chemotactic activity for endothelial cells (see at least the abstract). Moreover, Asahara et al taught that VEGF, GM-CSF, G-CSF, SCF and SDF-1 are capable of mobilizing HSCs from bone marrow to peripheral blood (see page 3966, col. 2, last three paragraphs).

3. The amount of direction or guidance provided

Apart from the exemplification showing that GM-CSF is capable of mobilizing circulating EPC in a mouse or a rabbit model, the instant specification fails to provide

sufficient guidance for a skilled artisan on how to use any effective amount of angiopoietin-2 or FLT-3 ligand to induce new blood vessels and for increasing endothelial progenitor cell frequency by at least about 20% as determined by a standard EPC isolation assay in any mammal having chronic or acute ischemia, let alone for any effective fragment thereof. Particularly, angiopoietin-2 is known to be a natural antagonist of angiopoietin-1 as evidenced by the teachings of Witzenbichler et al discussed above. Moreover, please note that the physiological art is recognized as unpredictable (MPEP 2164.03). Since the prior art at the effective filing date of the present application failed to provide any guidance on how to use any effective amount of angiopoietin-2 or FLT-3 ligand or any fragment thereof to attain the desired therapeutic effects in the methods as claimed, it is incumbent upon the present application to do so. Otherwise, it would have required undue experimentation for a skilled artisan to make and use the methods as broadly claimed.

As set forth in *In re Fisher*, 166 USPQ 18 (CCPA 1970), compliance with 35 USC 112, first paragraph requires:

> That scope of claims must bear a reasonable correlation to scope of enablement provided by specification to persons of ordinary skill in the are; in cases involving predictable factors, such as mechanical or electrical elements, a single embodiment provides broad enablement in the sense that, once imagined, other embodiments can be made without difficulty and their performance characteristics predicted by resort to known scientific laws; in cases involving unpredictable factors, such as most chemical reactions and physiological activity, scope of enablement varies inversely with degree of unpredictability of factors involved.

Accordingly, due to the lack of sufficient guidance provided by the specification regarding to the issues set forth above, the breadth of the claims, and the unpredictability of the physiological art to attain the desired therapeutic effects, it would

have required undue experimentation for one skilled in the art to make and use the instant broadly claimed invention.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 57 and 70 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. ***This is a new ground of rejection.***

Claim 57 is dependent on cancelled claim 53. Accordingly, the metes and bounds of the claim are not clearly determined because it is unclear what exactly Applicants intend to claim.

In claim 70, it is unclear what is encompassed by the phrase "and (3 (TGF-a and TFG-P)". Clarification is requested because the metes and bounds of the claim are not clearly determined. For example, is there such a molecule designated as "(3(TGF-a"? and TFG-P)?

Claim Rejections - 35 USC § 102

Claim 79 is rejected under 35 U.S.C. 102(b) as being anticipated by Takeshita et al. (J. Clin. Invest. 93:662-670, 1994; IDS) for the same reasons already set forth in the Office Action mailed on 5/4/2004 (page 4), and they are restated below. ***However, this***

is a new ground of rejection because claim 70 was inadvertently rejected instead of claim 79.

The claim is directed to a method for enhancing endothelial progenitor cell (EPC) mobilization in a mammal having chronic or acute ischemia, wherein the method comprises administering an effective amount of at least one hematopoietic factor sufficient to enhance the EPC mobilization in the mammal having the chronic or acute ischemia.

As defined by the present application, **a hematopoietic factor includes VEGF** (see page 21, lines 13-25). Takeshita et al. teaches a method of administering VEGF at doses of 500-1,000 ug as a single intraarterial bolus to the internal iliac artery of rabbits in which the ipsilateral fermral artery was excised to induce severe, unilateral hind limb ischemia (see abstract and the entire article). Since the disclosed method of Takeshita et al. has the same step as the instant claimed method (administering to a mammal having chronic or acute ischemia an effective amount of at least one hematopoeitic factor), and that the utilized dosage is within the preferred dosage range of contemplated by Applicants, enhancing endothelial progenitor cell mobilization would be an inherent result of the method taught by Takeshita et al.

Therefore, Takeshita et al. anticipate the instant claim.

Claims 50, 55-56, 58-63, 65-66, 79 and 82-84 are rejected under 35 U.S.C. 102(b) as being anticipated by Aharinejad et al. (Bone 16:315-324, 1995). ***This is a new ground of rejection.***

Aharinejad et al. teaches a method of administering highly purified recombinant human colony stimulating factor–1 (CSF-1 or M-CSF from Chiron Corp.) by subcutaneous injection at a daily dose of 10^6 units to osteopetrotic mutant rats (see page 315, col. 2, under the section entitled "Source and treatment of animals"). Aharinejad et al. observed that following CSF-1 treatment, angiogenesis increases sharply and proliferation of endothelial cells occurs both at the capillary tips and in deeper, larger vessels of the mutant metaphysis. Aharinejad et al. further teaches that neoangiognesis seen after the CSF-1 treatment was present in peripheral capillary regions beneath the growth plate and in endothelial cells lining the bone marrow sinuses, and that cast preparations of the treated mutants showed not only sprouts but also that their supplying vessels were increased in number compared to the untreated mutant animals (page 322, the entire col. 1).

Aharinejad et al also discloses that compared to untreated normal rats, untreated mutants (osteopetrotic mutant rats) showed little bone growth or angiogenesis (see at least the abstract), and therefore osteopetrotic mutant rats can be considered to have a chronic ischemic condition. Please also note that as taught by the instant specification, ischemic tissue can arise by nearly any means including a surgical manipulation or a medical condition (page 8, lines 5-7). Following treatment with CSF-1 or M-CSF, the osteopetrotic condition in toothless rats greatly improves and growth is accelerated as described above.

Because the method of Aharinejad et al. has the same method step and the same starting materials, it is inherent that the method of Aharinejad et al also produces the same desired effects in the methods as claimed.

Accordingly, the reference anticipates the instant claims.

Claim Rejections - 35 USC § 103

Claims 50, 55-56, 58-63, 65-66, 68, 70 and 82-84 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hammond et al. (U.S. Patent 5,880,090; Cited previously) in view of Asahara et al. (Science 275:964-967, 1997; Cited previously). ***This is a modified rejection and the following rejection is made in light of the 1.131 Declaration filed on 2/17/04.***

Hammond et al. teaches that upon administering an agent including stem cell factor (SCF), granulocyte-macrophage colony-stimulating factor (GM-CSF) and granulocyte colony-stimulating factor (G-CSF) into a graft recipient, bone marrow-derived CD34+ endothelial progenitor cells are mobilized into the blood stream (increase in the concentration of the progenitor cells) and to enhance the endothelialization of synthetic vascular grafts (See abstract and example 3 in column 9). Hammond et al. also teaches that more than one endothelialization-promoting agent (e.g., fibroblast growth factors, VEGF, angiopoietin-1 described by Suri et al) may be administered concomitantly, and the agent may be administered to the intended graft recipient as much as seven days prior to implantion of the graft, or may begin on the same day as graft implantation (see col. 3, lines 57-67; col. 4, lines 32-40). An

exemplified used dosage for G-CSF is from about 5ug to 15 ug/kg body weight for a total of 3 to 5 days (col. 4, lines 24-31), which is within the preferred dosage range of vascularization modulating agents of the presently claimed invention (1 ug/kg/day to about 100 ug/kg/day).

Hammond et al. does not teach specifically a method for inducing formation of new blood vessels or enhancing EPC mobilization in a mammal having chronic or acute ischemia using the aforementioned agents (e.g., SCF, G-CSF, GM-CSF).

However, Hammond et al. noted that Asahara et al. have shown CD34+ endothelial cell populations are capable of differentiating into endothelial-like cells and the circulating CD34+ or Flk-1+ cells may participate in the repair of ischemic tissue (column 3, lines 28-37). In animal models of ischemia (mouse and rabbit models of induced unilateral hindlimb ischemia), Asahara et al. already teaches that syngeneic or autologous endothelial cell progenitors home in and they are incorporated into capillaries and small arteries in the neovascular zones of the induced ischemic limb (See abstract and page 966).

Accordingly, at the time of the instant invention it would have been obvious for an ordinary skilled artisan to modify the method disclosed by Hammond et al. by administering into a mammal having an chronic or acute ischemia instead of a recipient of a synthetic vascular graft an agent selected from the group consisting of SCF, GM-CSF and G-CSF to mobilize an effective level of bone marrow-derived endothelial progenitors to home into sites of active angiogenesis to repair ischemic tissues by forming new blood vessels in light of the teachings of Asahara et al.

An ordinary skilled artisan would have been motivated to carry out the above modification to avoid the tedious and time-consuming isolation and purification of progenitor endothelial cells. Since the modified method has the same method step and same active components (e.g., GM-CSF, G-CSF, SCF) with an effective dosage within the preferred dosage range of vascularization modulating agents used in the presently claimed invention, the modified method is indistinguishable from the methods as claimed.

An ordinary skilled artisan would have a reasonable expectation of success in light of the teachings of Hammond et al., Asahara et al., and coupled with a high level of skill possessed by an ordinary skilled artisan in the relevant art.

Therefore, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Response to Arguments

With respect to the above rejection, Applicant's arguments in the Amendment filed on 10/20/03 (pages 8-10) have been fully considered, but they are respectfully found to be not persuasive for the following reasons.

Applicants argue basically that a Rule 131 Declaration is sufficient for antedating a reference if it can establish possession of subject matter falling within the claimed invention such that the claim at issue reads on. Additionally, Applicants further argue that before Hammond's priority date Applicants learned that one could induce new

blood vessels in a mammal having ischemia by using GM-CSF as well as other suitable cytokines.

The Declaration filed on 2/17/04 under 37 CFR 1.131 has been considered but is ineffective to overcome the Hammond reference, with respect to hematopoietic factor other than GM-CSF.

The evidence submitted is insufficient to establish a conception of the invention prior to the effective date of the Hammond reference. While conception is the mental part of the inventive act, it must be capable of proof, such as by demonstrative evidence or by a complete disclosure to another. Conception is more than a vague idea of how to solve a problem. The requisite means themselves and their interaction must also be comprehended. See *Mergenthaler v. Scudder*, 1897 C.D. 724, 81 O.G. 1417 (D.C. Cir. 1897). This is because prior to September 19, 1997 apart from GM-CSF, Applicants did not conceive specifically, let alone demonstrate, that SCF, SDF-1, G-CSF, M-CSF, angiopoeitin-1, angiopoietin-2 or FLT-3 ligand is capable of mobilizing endothelial progenitor cells for the induction of new blood vessels in a mammal having chronic or acute ischemia. Furthermore, it should be noted that different members of a broad genus of a cytokine or a hematopoeitic factor are structurally distinct one from the others, and that each has different biochemical properties one from the others.

The evidence submitted is insufficient to establish diligence from a date prior to the date of reduction to practice of the Hammond reference to either a constructive reduction to practice or an actual reduction to practice. Apart from the demonstration that GM-CSF is capable of mobilizing endothelial progenitor cells, there was no

evidence indicating or suggesting that Applicants conceived or demonstrated that SCF, SDF-1, G-CSF, M-CSF, angiopoeitin-1, angiopoietin-2 or FLT-3 ligand is capable of mobilizing endothelial progenitor cells for the induction of new blood vessels in a mammal having chronic or acute ischemia.

The evidence submitted is insufficient to establish applicant's alleged actual reduction to practice of the invention in this country or a NAFTA or WTO member country after the effective date of the Hammond reference. There was no evidence indicating that Applicants demonstrated that SCF, SDF-1, G-CSF, M-CSF, angiopoeitin-1, angiopoietin-2 or FLT-3 ligand is capable of mobilizing endothelial progenitor cells for the induction of new blood vessels in a mammal having chronic or acute ischemia after the effective filing date of the Hammond reference.

Accordingly, claims 50, 55-63, 65-66, 68, 70, 79 and 82-84 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hammond et al. in view of Asahara et al. for the reasons set forth above.

Claim 67 is rejected under 35 U.S.C. 103(a) as being unpatentable over Hammond et al. (U.S. Patent 5,880,090; Cited previously) in view of Asahara et al. (Science 275:964-967, 1997; Cited previously) as applied to claims 50, 55-56, 58-63, 65-66, 68, 70 and 82-84 above, and further in view of either Franco (U.S. Patent 4,296,100; Cited previously) or Kawakami et al. (Brain Res. 697:104-111, 1995; Cited previously). ***This is a new ground of rejection.***

The combined teachings of Hammond et al and Asahara et al have been discussed above. However, none of the references teaches specifically that the ischemic tissue comprises a heart or brain tissue.

At the effective filing date of the present application, Franco already taught the use of an angiogenic factor, FGF, to treat an area in the heart of a patient subjected to ischemic heart disease to maintain viability in that area for a sustained time period to salvage said area (See examples 1 and 2, and the claims).

Kawakami et al also taught a local injection of b-FGF into the evacuated cavity in an experimental rat model of intracerebral hemorrahage resulting from early removal of a mass lesion, yielded a protective effect against neuronal damage in CA1 pyramidal cells (probably from ischemia due to the transient mass lesion in the caudate nucleus) and an increased angiogenesis in the evacuated cavity wall (See abstract, and page 108, column 2, fourth paragraph).

It would have been obvious for an ordinary skilled artisan to further modify the teachings of Hammond et al and Asahara et al by treating a mammal having an ischemic heart or brain tissue in light of the teachings of either Franco or Kawakami et al.

An ordinary skilled artisan would have been motivated to carry out the above modification because a mammal having an ischemic heart tissue or brain tissue has been treated with an angiogenic factor such as FGF or bFGF as taught by Franco and Kawakami et al., respectively.

An ordinary skilled artisan would have a reasonable expectation of success in light of the teachings of Hammond et al., Asahara et al., and either Franco or Kawakami et al., and coupled with a high level of skill possessed by an ordinary skilled artisan in the relevant art.

Therefore, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

An embodiment of claims 50, 55-56, 58-63, 65-66, 68, 70 and 82-84 (drawn to stromal cell derived factor or SDF-1) are rejected under 35 U.S.C. 103(a) as being unpatentable over Hammond et al. (U.S. Patent 5,880,090; Cited previously) in view of Asahara et al. (Science 275:964-967, 1997; Cited previously) as applied to claims 50, 55-56, 58-63, 65-66, 68, 70 and 82-84 above, and further in view of Aiuti et al. (J. Exp. Med. 185:111-120,1997). ***This is a new ground of rejection.***

The combined teachings of Hammond et al and Asahara et al have been discussed above. However, none of the references teaches specifically the use of SDF-1, even though Hammond et al teaches clearly using any agent capable of increasing the concentration in the recipient's blood of bone marrow-derived endothelial progenitors.

However, at the effective filing date of the present application Aiuti et al already taught that the chemokine SDF-1 is a chemoattractant for human CD34+ hematopoietic progenitor cells and it is capable of mobilizing of CD34+ progenitors to peripheral blood (see at least the abstract).

It would have been obvious for ordinary skilled artisan to further modify the teachings of Hammond et al and Asahara et al by using SDF-1 as an agent for increasing the concentration in the recipient's blood of bone marrow-derived endothelial progenitors or CD34+ progenitors in light of the teachings of Aiuti et al.

An ordinary skilled artisan would have been motivated to carry out the above modification because Aiuti et al already clearly demonstrated that SDF-1 is a chemoattractant for human CD34+ hematopoietic progenitor cells and it is capable of mobilizing of CD34+ progenitors to peripheral blood.

An ordinary skilled artisan would have a reasonable expectation of success in light of the teachings of Hammond et al., Asahara et al., Aiuti et al., and coupled with a high level of skill possessed by an ordinary skilled artisan in the relevant art.

Therefore, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

New claim 84 is rejected under 35 U.S.C. 103(a) as being unpatentable over Takeshita et al. (J. Clin. Invest. 93:662-670, 1994; IDS) for the same reasons already set forth in the Office Action mailed on 5/4/2004 (pages 5-8), and it is restated below.

Takeshita et al. teaches a method of administering VEGF at doses of 500-1,000 ug as a single intraarterial bolus to the internal iliac artery of rabbits in which the ipsilateral fermoral artery was excised to induce severe, unilateral hind limb ischemia (see abstract and the entire article). Statistically significant augmentation of collateral vessel development by angiography as well as the number of capillaries by histology,

and greater amelioration of the hemodynamic deficit in the ischemic limb were observed in animals receiving VEGF than in non-treated controls.

Takeshita et al. does not teach explicitly a method of administering VEGF to a mammal having chronic or acute ischemia, **wherein the mammal is a rodent or a primate**.

However, Takeshita et al. teaches that the findings in the disclosed rabbit ischemic hind limb model establish proof of principle for the concept that the angiogenic activity of VEGF is sufficiently potent to achieve therapeutic benefit, and that such a strategy might ultimately be applicable **to patients with severe limb ischemia secondary to arterial occlusion disease** (see abstract).

Accordingly, at the effective filing date of the present application it would have been obvious for an ordinary skill artisan to modify the method of Takeshita et al. by administering VEGF at doses of 500-1,000 ug to a human patient with severe limb ischemia to attain therapeutic angiogenesis. The modified method of Takeshita et al. is indistinguishable from the presently claimed invention because it has the same step administering to a rodent or a primate having chronic or acute ischemia an effective amount of a VEGF, and that the utilized VEGF dosage is within the preferred dosage range of contemplated by Applicants.

An ordinary skilled artisan would have been motivated to carry out the above modification because Takeshita et al. teaches clearly that the findings in the disclosed rabbit ischemic hind limb model establish proof of principle for the concept that the angiogenic activity of VEGF is sufficiently potent to achieve therapeutic benefit, and that

such a strategy might ultimately be applicable to patients with severe limb ischemia secondary to arterial occlusion disease.

An ordinary skilled artisan would have a reasonable expectation of success based on the findings of Takeshita et al., and the high level of skill of an ordinary skilled artisan in the art of angiogenesis at the effective filing date of the present application.

Therefore, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Double Patenting

Claims 50, 52, 55-56, 58-63, 65-67, 70, 79 and 82-84 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 3-4 and 11 of U.S. Patent No. 5,980,887. ***This is a modified rejection.***

Although the conflicting claims are not identical, they are not patentably distinct from each other because a method for inducing the formation of new blood vessels in an ischemic tissue in a patient (usually a human patient) in need thereof (e.g., treatment for cerebrovascular ischemia, renal ischemia, pulmonary ischemia, limb ischemia, ischemic cardiomyopathy as well as myocardial ischemia) or a method for treating an injured blood vessel in a patient in need thereof, said method **comprises** the same step of administering to the patient an endothelial mitogen that includes a vascular endothelial growth factor, granulocyte/macrophage CSF, macrophage CS or a colony stimulating factor in the issued U.S. Patent 5,980,887 anticipate the claimed genus of a method for inducing formation of new blood vessels in a rodent or a primate having

chronic or acute ischemia, wherein the method **comprises** administering to the mammal an effective amount of a vascular endothelial growth factor (VEGF) or a hematopoietic factor sufficient to form the new blood vessels in the mammal, and increasing endothelial progenitor cell (EPC) frequency, wherein the hematopoeiticfactor is a GM-CSF, SCF, SDF-1,G-CSF, M-CSF, angiopoietin-1, angiopoietin-2, FLT-3 ligand or an effective fragment thereof; and a method for enhancing EPC in a mammal having chronic or acute ischemia **comprising** administering an effective amount of at least one hematopoietic factor sufficient to enhance the EPC mobilization in the mammal in the application being examined and, therefore, a patent to the genus would, necessarily, extend the rights of the species or sub-, should the genus issue as a patent after the species of sub-genus.

Claims 50, 52, 55-56, 58-63, 65-68, 70, 79 and 82-84 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 49-52, 54-59, 65 and 68 of the copending Application No. 10/696,391. ***This is a modified rejection.***

Although the conflicting claims are not identical, they are not patentably distinct from each other because a method for inducing new blood vessel growth in myocardial tissue of a mammal in need of such treatment, including a human, said method **comprises** the same step of administering to the mammal an effective amount of at least one angiogenic factor or an effective fragment thereof, thereby inducing new blood vessel growth in the myocardial tissue of the mammal, and increasing the frequency of

endothelial progenitor cells in the mammal, wherein the angiogenic factor includes VEGF, SCF, GM-CSF, M-CSF or a fragment thereof in the copending Application No. 10/696,391 anticipate the claimed genus of a method for inducing formation of new blood vessels in a rodent or a primate having chronic or acute ischemia, wherein the method **comprises** administering to the mammal an effective amount of a vascular endothelial growth factor (VEGF) or a hematopoietic factor sufficient to form the new blood vessels in the mammal, and increasing endothelial progenitor cell (EPC) frequency, wherein the hematopoietic factor is a GM-CSF, SCF, SDF-1,G-CSF, M-CSF, angiopoietin-1, angiopoietin-2, FLT-3 ligand or an effective fragment thereof; and a method for enhancing EPC in a mammal having chronic or acute ischemia **comprising** administering an effective amount of at least one hematopoietic factor sufficient to enhance the EPC mobilization in the mammal in the application being examined and, therefore, a patent to the genus would, necessarily, extend the rights of the species or sub-, should the genus issue as a patent after the species of sub-genus.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claims 50, 52, 55-56, 58-63, 65-67, 79 and 82-84 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 49 and 58-60 of the copending Application No. 10/714,574. ***This is a modified rejection.***

Although the conflicting claims are not identical, they are not patentably distinct from each other because a method for treating ischemic myocardial tissue of a mammal in need of such treatment, including a human, said method **comprises** the same step of administering to the mammal an effective amount of at least one of SCF or CSF (including GM-CSF) or an effective fragment thereof, in the copending Application No. 10/714,574 anticipate the claimed genus of a method for inducing formation of new blood vessels in a rodent or a primate having chronic or acute ischemia, wherein the method **comprises** administering to the mammal an effective amount of a vascular endothelial growth factor (VEGF) or a hematopoietic factor sufficient to form the new blood vessels in the mammal, and increasing endothelial progenitor cell (EPC) frequency, wherein the hematopoietic factor is a GM-CSF, SCF, SDF-1,G-CSF, M-CSF, angiopoietin-1, angiopoietin-2, FLT-3 ligand or an effective fragment thereof; and a method for enhancing EPC in a mammal having chronic or acute ischemia **comprising** administering an effective amount of at least one hematopoietic factor sufficient to enhance the EPC mobilization in the mammal in the application being examined and, therefore, a patent to the genus would, necessarily, extend the rights of the species or sub-, should the genus issue as a patent after the species of sub-genus.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Conclusion

Claims 72-78 are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Quang Nguyen, Ph.D., whose telephone number is (571) 272-0776.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's SPE, Dave Nguyen, may be reached at (571) 272-0731.

To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1633; Central Fax No. (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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